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EXAMINER	
BALLARD, KIMBERLY	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,060	ARTAVANIS-TSAKONAS ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *34,91-94,98,100 and 117-129* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *34,91-94,98,100 and 117-129* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claims 34 and 100 have been amended, claims 96, 97, 99, 101-106, 108-111 and 113-116 have been canceled, and new claims 117-129 have been added as requested in the amendment filed November 4, 2011. Following the amendment, claims 34, 91-94, 98, 100 and 117-129 are pending in the present application.

2. Claims **34, 91-94, 98, 100** and **117-129** are under examination in the current office action.

Withdrawn Claim Rejections

3. Any objection or rejection of record pertaining to any of claims 96, 97, 99, 101-106, 108-111 or 113-116 is rendered moot on account of these claims having been canceled by applicant.

4. The rejection of claims 34, 91-94, 98 and 100 under 35 U.S.C. 112, first paragraph (written description), is withdrawn in view of applicant's amendments to the claims. The anti-Notch antibody of the present claims is reasonably described by the specification as filed.

5. The rejection of claims 34 and 91-94 under 35 U.S.C. 112, second paragraph (indefiniteness), is withdrawn in view of applicant's amendment to the claims.

Maintained Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 34, 91-94, 98, 100 and 117-129 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for reasons of record for claims 34, 91-94, 98 and 100 and is further applied to new claims 117-129.

The claims, as amended, are drawn to a method of treating a disease or disorder in a human, wherein the disease or disorder is a malignancy characterized by increased Notch activity or increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample, the method comprising administering to a human in need of such treatment a therapeutically effective amount of an antibody to a human Notch protein, or a fragment of said antibody containing the idiotype thereof, which antibody or fragment inhibits binding of the human Notch protein to a Delta protein or to a Serrate protein.

The basis for this rejection is already of record and therefore will not be reiterated here.

Response to Arguments

8. In the response filed November 4, 2011, Applicant argues that with respect to breadth of malignancies being treated, the specification clearly discloses that the increased expression of human Notch protein in human tumors was identified through the quantitation of the amount of binding by an anti-human Notch antibody. That is, Applicant asserts, the tumors were actually determined to have increased expression of a molecule with Notch antigenicity. Applicant submits that the malignancy recited in the claims is similarly defined in part as being characterized by increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample. According to Applicant, the breadth of the claims is thus consistent with the data of the specification.

Further, Applicant submits that the post-filing reference by Aste-Amézaga et al. (*PLoS One*, 2010; 5:e9094; attached with Applicant's response and now listed on present form PTO-892 as a reference of record) "demonstrates that most of the selected, high affinity antibodies to the Notch1 extracellular domain inhibited binding between the Notch1 ectodomain and a Delta protein (Dll4)... The antibodies that did not inhibit such binding recognized the NRR domain rather than the EGF-like repeat domain (the LBD [ligand-binding domain])." Applicant also point out that the Li et al. reference (*J Biol Chem*, 2008; 283:8046-8054; cited previously) still demonstrates that antibodies

specific for the EGF-repeat region of Notch3 inhibited Notch3 activation and that such antibodies were only described as weak antagonists of JAGGED1 (a mammalian Serrate)- and Dll4 (a Delta)-induced Notch3 signaling in contrast to the more potent inhibition of antibodies directed against the NRR domain. Accordingly, Applicant asserts that they have provided evidence showing that anti-Notch antibodies are capable of inhibiting binding between a human Notch protein and its ligand, a Delta or Serrate protein, that activated Notch function is associated with malignancy, and that antagonizing the function of a Notch protein should have anti-tumor therapeutic value. Taken together, Applicant thus argues that this evidence is sufficient to convince one skilled in the art of the asserted utility, i.e., that an antibody to a human Notch protein that inhibits binding of a human Notch protein to a ligand (a Delta or Serrate protein) can be used to treat a malignancy.

9. Applicant's arguments have been fully considered but they are not persuasive. Note that Applicant is correct in pointing out at pp. 8-9 that those portions of the rejection of record pertaining to toporythmic proteins/genes or Notch antisense oligonucleotides is moot in view of the claim amendments. However, in contrast to Applicant's assertions regarding the scope of the claimed malignant disease or disorder to be treated, it is again noted that the breadth of the claims is still quite broad. The claims encompass the treatment of any malignancy characterized by increased Notch activity or expression of a human Notch protein or derivative thereof. The specification at page 49 describes derivatives of Notch as including, but not limited to, "those peptides which are substantially homologous to Notch or fragments thereof, or whose

encoding nucleic acid is capable of hybridizing to a *Notch* nucleic acid sequence." This statement and others within the instant application provide for great latitude in what constitutes a "Notch derivative".

The recitation in the present claims that the Notch derivative is "capable of being bound by an antibody to a human Notch protein" does not serve to limit the scope of claimed malignancy, because, as stated previously, antibodies can have substantial variations in affinity for a given antigen, and may have cross-reactivity with unrelated protein molecules. In other words, an antibody to a human Notch protein could also be cross-reactive with other proteins unrelated to Notch, which may bear little to no homology to Notch but for a common antigenic epitope to which the antibody binds. Such an unrelated protein would be capable of being bound by an anti-Notch antibody as recited in claim 34. And in view of the definition of "Notch derivative" provided in the instant specification, which also states that derivatives include those containing "all or part of the amino acid sequence of a Notch protein including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change" (p. 49, lines 4-8), it can seen that the scope of the instant claims is quite broad with respect to how the malignancy is characterized. The broadest reasonable interpretation of the claims would thus encompass the treatment of any malignant disease or disorder having increased expression of any protein comprising a peptide sequence that bears some homology to a fragment of a human Notch protein. Such a fragment could be as small as an antibody's binding

epitope, such as a sequence of about 5-6 amino acid residues, which thus would be capable of being bound by the recited antibody.

Additionally, the Aste-Amézaga et al. reference submitted by Applicant evidences that just because a malignancy is characterized by increased Notch activity or expression, it still may not be amenable to treatment with an anti-Notch antibody that inhibits binding of Notch to a Delta or Serrate protein. In particular, Aste-Amézaga notes that Notch1 activating mutations in the negative regulatory region (NRR) account for 55-60% of T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) cases (see p. 2, left column). Importantly, these mutations cause increased ligand-independent Notch activation. That is, the activation of Notch by binding to its ligands, Delta or Serrate, is not a factor in these malignancies. Aste-Amézaga notes that antibodies directed against the ligand binding domain (LBD, i.e., the EGF-like repeat domain) of Notch had no effect on inhibiting signaling by Notch1 receptors harboring T-ALL-associated mutations (i.e., ligand-independent Notch signaling) (see p. 9, left column). Therefore, at best the claimed antibodies would only be capable of eliciting a therapeutic effect in malignancies characterized by increased *ligand-dependent* Notch activity or expression.

Moreover, the scope of the claims includes the therapeutic use of an antibody directed to any human Notch protein. As noted previously, the nature of the invention is quite complex and the unpredictability in the art is high. In mammals (including humans), the key components of the Notch pathway comprise four Notch receptors (N1-N4) and six ligands (Dll1, Dll3, Dll4, Dlk, Jag-1 and Jag-2) (see Nickoloff et al. [cited previously], and section 3.1 on p. 4371 of review by Wu et al. [*Frontiers Biosci.* 2007;

12:4370-4383]). The instant specification provides for information only for the human Notch1 isoform (i.e., TAN1, hN1); the existence of Notch2, Notch3 and Notch4 were unknown at the time of filing, as were the complex interactions between the different Notch receptors and their ligands. Even today, the art acknowledges that many aspects of Notch signaling are poorly understood, particularly in the role of tumorigenesis. The presence of different Notch isoforms in different cancers, their individual effects and the functional relationship between each of the isoforms add to the complexity of the signaling pathways. Notch-induced transformation of tumor cells is further confounded by the fact that different Notch receptors are involved in different stages of tumor progression, and the receptors are shown to function as downstream mediators of each other (Nickoloff, p. 6602).

Even more complex, Wu et al. (2007) notes that Notch has two roles in tumorigenesis: as an oncogene or a tumor suppressor, which appear to be dependent on the cellular context and crosstalk with other signaling pathways (see p. 4375, right column, top paragraph). For example, Notch1 and Notch2 can have opposite effects on the growth of the same type of tumors (see p. 4375, paragraph spanning left and right columns). In embryonal brain tumor cell lines, cell proliferation, soft agar colony formation, and xenograft growth were all *promoted* by Notch2 and *inhibited* by Notch1 (specifically, see Fan et al. (2004) *Cancer Res.* 64:7787-7793; cited by Wu et al.) Notably, Notch2 activity and expression was increased in these tumor cells, and therefore these tumors would meet the limitation of a disease or disorder that is "a malignancy characterized by increased Notch activity or expression of a human Notch

protein or of a Notch derivative" of the present claims. However, in this instance, the limited guidance provided in the present specification would have been insufficient for treatment of such a malignancy mainly because the only antibodies that could be produced according to the instant invention would be those directed against Notch1. In the case of this type of malignancy, antagonism of Notch1 by an antibody that inhibits ligand binding to Notch1, would likely *enhance* tumor progression, as it would bias the tumors toward unchecked Notch2 (tumorigenic) activity. Additionally, Wu notes instances in which Notch1 functions as a tumor suppressor, such as in human tongue carcinoma and in HPV-positive cervical cancer cells (see p. 4375, left column). Again, antibody mediated antagonism of Notch1 in these malignancies would not be reasonably predicted to be therapeutically beneficial.

Moreover, MPEP § 2164.01 states that "[a]ny analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" (emphasis added by the Examiner). And MPEP § 2164.05 states that "[t]o overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing" (emphasis in original). In the previous office action, the examiner indicated that the specification and the prior art do not teach any working examples nor sufficient guidance to indicate that the administration of an anti-Notch antibody can be used to treat a malignancy in a

subject without undue experimentation. The limited teachings of the specification are not adequate guidance, but are merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Furthermore, MPEP § 2164.03 states that:

> The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology.")

The Aste-Amézaga reference provided by applicant was published in 2010, which is over 18 years *after* the earliest priority date sought by present invention. This, if nothing else, goes to evidence that at the time of filing, the present invention does not have an enabling disclosure. The specific monoclonal antibodies utilized by Aste-Amézaga et al. are not referred to or taught by the specification of the instant application. A later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling (MPEP § 2164.05(a)). There is insufficient guidance in the present specification as filed relating to the therapeutic use of anti-Notch antibodies for treatment of malignancies generally, and no guidance or evidence

whatsoever directed to the therapeutic use of antibodies specific for the different Notch isoforms, which antibody specificity would be necessary to facilitate the inhibition of Notch-related growth and/or proliferation in various types of tumor cells and malignancies as discussed above. Accordingly, the scope of patent protection sought by Applicant as defined by the claims fails to reasonably correlate with the scope of enabling disclosure set forth in the specification. Therefore, the present rejection is maintained.

Conclusion

10. No claims are allowed.

11. Applicant's amendment necessitated the new references presented in this Office action. Such references were relied upon only to counter Applicant's arguments (and newly submitted evidentiary reference) as well as to discuss amended limitations of the claims, and do not in any change the basis of the rejection of record. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is (571)272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646